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REVIEW ARTICLE

Behavioral and psychological symptoms of dementia associated with vascular impairment: a systematic review and meta-analysis

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Objective: Vascular cognitive impairment (VCI) is a major cause of cognitive decline associated with vascular brain injury. Behavioral and psychological symptoms of dementia (BPSD) are common, but their prevalence across VCI subtypes remains unclear. This study examines the prevalence of BPSD in different VCI subtypes.
Methods: A systematic review and meta-analysis were conducted following PRISMA guidelines. Studies assessing BPSD in patients with VCI were retrieved from PubMed, Embase, and Web of Science. Studies were eligible if they used the Neuropsychiatric Inventory (NPI) to evaluate symptoms. Pooled prevalence rates for each NPI domain were calculated using a random-effects model.
Results: Thirty-five studies (n=5,805) were included. In unspecified VCI, apathy (54.29%), depression (43.48%), and irritability (38.76%) were most common. Subcortical VCI was associated with higher apathy (62.01%), depression (52.11%), and irritability (44.73%). Mixed dementia featured increased apathy (61.65%), depression (45.68%), sleep disturbances (44.63%), and more hallucinations (26.64%). VCI non-dementia (VCI-ND) was associated with depression (44.97%), irritability (32.75%), and anxiety (30.07%).
Conclusion: BPSD are prevalent across VCI subtypes but vary. Mixed dementia features more hallucinations and sleep disturbances, likely due to overlapping vascular and neurodegenerative pathology. Apathy and agitation in subcortical VCI may reflect vascular burden. Further research is warranted to clarify underlying neurobiological mechanisms.

Systematic review registration: PROSPERO CRD42024587171

Keywords: Vascular cognitive impairment; vascular dementia; mixed dementia; neuropsychiatric inventory

Introduction

Dementia is a major neurocognitive disorder that comprises different pathologic substrates and cognitive presentation syndromes. It is estimated that 55 million people worldwide currently live with dementia, and this number is estimated to grow by 10 million new cases each year.[1] Behavioral and psychological symptoms of dementia (BPSD) are reported in about 60-90% of these patients and increase the risk of hospitalization, caregiver burden, and patient distress.[2] Several studies have demonstrated considerable variation in BPSD across different etiologies, such as vascular cognitive impairment (VCI), Alzheimer's disease (AD), Lewy bodies disease (LBD), and frontotemporal dementia (FTD).[3,4] Historically, this variance proved essential in understanding the natural history and differential diagnosis of cognitive syndromes and their proper management in clinical care. Although VCI is considered the second most common cause of dementia after AD, BPSD have not been thoroughly investigated in this condition.

VCI can be defined as any cognitive or behavioral impairments related to a vascular brain injury, such as ischemia or hemorrhage, and is commonly classified as stroke-related, mixed, cortical multi-infarct dementia, and subcortical ischemic vascular dementia.[5,6] VCI can also

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be classified according to its stage, ranging from asymptomatic (e.g., brain at risk) to mild cognitive impairment (MCI) to vascular dementia (VaD).[6] On this basis, it is hypothesized that BPSD may vary according to the degree and etiology of the underlying VCI. For instance, apathy and depression are commonly associated with the progression of white-matter hyperintensities (WMH), leading to subcortical network disruption.[7-14] However, the frequency and neurobiology of other commonly reported BPSD, such as anxiety, sleep disturbances, and irritability, are poorly understood, with fewer studies investigating their association with vascular burden.[15,16]

Even though a previous meta-analysis investigated the general range of BPSD among all-cause dementia patients, the current literature lacks an investigation of VCI using a similar analytical approach.[9] Supporting the idea that the distinction of BPSD profiles might elucidate their pathological substrates, with clinical implications, we aimed to determine the prevalence of BPSD in VCI subtypes and stages and how their occurrence differed. The pathophysiology of these symptoms was approached narratively.

Methods

Registration and protocol

While conducting this research, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and recommendations from the Cochrane Collaboration.[17] This review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) under CRD42024587171 to ensure further transparency. No protocol for this study was published beforehand.

Eligibility criteria

We searched for articles that assessed the prevalence of neuropsychiatric symptoms in patients with a diagnosis of VCI. Randomized controlled trials, cohort studies, and cross-sectional studies were included. Also, patients with a VaD diagnosis were required to have met the criteria defined by the third, fourth, or fifth edition of the DSM, the National Institute of Neurological Disorders and Stroke-Association International pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN), or the Brazilian Academy of Neurology.[6,18-21] Furthermore, studies were only eligible if they employed the Neuropsychiatric Inventory (NPI)[22] to assess and categorize BPSD.

We excluded all records that did not meet the study design criteria, such as reviews, meta-analyses, case reports, opinion pieces, and guidelines. We also excluded abstracts and studies with overlapping populations. No restrictions were set concerning publication date, language, or geographic region where the research was conducted.

Search strategy

In May 2024, the reviewers comprehensively searched the PubMed, Embase, and Web of Science databases. To compose the search strategy and follow the specific search rules of each database, Medical Subject Headings (MeSH) terms and keywords were adapted accordingly. Terms were combined by Boolean operators (AND, OR), as can be seen in full detail in Supplementary Table S1. To ensure completeness, we also assessed the references of included articles and published literature reviews in search of eligible records.

After searching the databases and reviewing references from the literature, we used Rayyan reference management software to organize the retrieved records and eliminate duplicate entries.[23] Then, two reviewers (APS and CBALS) independently screened the titles and abstracts of the remaining studies against our predetermined eligibility criteria. A third reviewer (AOML) resolved any disagreements.

Data extraction

To summarize the main findings, the authors independently extracted data from the included articles: authors and year of publication, study design, and baseline clinical data of the patient sample, encompassing type of VCI, age, years of education, Mini-Mental State Examination (MMSE) score, and Clinical Dementia Rating (CDR) scale. The endpoint of interest was the proportion of patients presenting each of the symptoms that compose the NPI at baseline, namely 1) delusions, 2) hallucinations, 3) agitation/aggression, 4) depression/dysphoria, 5) anxiety, 6) elation/euphoria, 7) apathy/indifference, 8) disinhibition, 9) irritability/lability, 10) aberrant motor behavior, 11) sleep and nighttime disorders, and 12) appetite and eating disorders.

Patients were divided into four different groups. If the study applied the aforementioned diagnostic criteria but did not subclassify VaD, the patients were put in the unspecified (general) VCI group. Those with evidence of subcortical impairment were put in the subcortical VaD group. Patients with a combination of VaD and any other etiology of dementia, such as AD, FTD, or LBD, were categorized as having mixed dementia, as proposed by the Vascular Impairment of Cognition Classification Consensus Study (VICCCS).[5] Patients with evidence of VCI who met the DSM or NINDS-AIREN criteria for MCI or non-dementia VCI were deemed as having VCI non-dementia (VCI-ND). All data were exported to a Microsoft Excel spreadsheet and reviewed to ensure accuracy and completeness.

Quality and methodological assessment

Four reviewers (APS, CBALS, BHCCF, MMCR) individually assessed the methodological quality of the included studies. The tool of choice for randomized controlled trials was the Cochrane Collaboration's risk of bias tool (RoB 2).[24] At the same time, cohort and cross-sectional studies were evaluated using the U.S. National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational and Cross-Sectional Studies.[25] Study quality was classified as poor, fair, or good according to potential bias or flaws in the studies' methods.

The reviewers also evaluated the possibility of publication bias and small-study effects by employing funnel plots and the Thompson-Sharp linear regression test.[26]

Statistical analysis

To obtain a truthful estimate of the overall prevalence of BPSD in patients with VCI, a random-effects model single-arm meta-analysis was performed using the "meta" and "metaphor" packages in R (version 4.3.2).[27] The reported prevalences from the studies for each symptom of the NPI were subjected to a logit transformation. The weights for each study were calculated according to the inverse variance method. The extent of heterogeneity was evaluated using the τ^2 statistic, which quantifies the variability in true effects, and the I^2 statistic, which indicates the proportion of variation attributable to heterogeneity.[28] Heterogeneity was deemed significant if the p-value was below 0.10 or if I^2 exceeded 25%.

To investigate how much each study influenced the overall result and heterogeneity, a sensitivity analysis by the leave-one-out method was conducted. Also, to identify the correlation of the sample's specific baseline characteristics with the observed results, a meta-regression was performed for those endpoints with at least 10 observations, ensuring adequate statistical power. The logit-transformed prevalences and their respective 95% confidence and prediction intervals were back-transformed for presentation.

Results

Search results and characteristics of the included studies

Our search found 986 papers, of which 487 were excluded for being duplicates. Of the remaining 499 reports, 75 were eligible for full-text review after title and abstract screening. After applying our eligibility criteria, 35 studies were included in the systematic review and meta-analysis, comprising 47 study populations and 5,805 participants. A step-by-step flow diagram of our search strategy is given in Figure 1.[3,4,29-61]

Of the 35 included studies, 32 were cross-sectional, two were prospective cohort studies, and one was a randomized controlled trial. Regarding the 47 study populations included in this systematic review and meta-analysis, we identified 30 populations with unspecified (general) VCI, seen with subcortical impairment; seven with mixed-dementia impairment; and three with VCI-ND. These populations were distributed across 21 countries and four continents, predominantly Europe (11 countries) and Asia (eight countries). Concerning sample characteristics, mean age ranged from 58.05 to 81.50 years; years of education, from 2.84 to 12.80 years; and MMSE and CDR scores, from 13.22 to 25.80 and 0.68 to 1.98, respectively. Study characteristics and patient data are reported in Table 1. The results by NPI domains for each cognitive impairment type are summarized in Table 2.

Quality assessment

Overall, five studies were assessed as having good quality, 27 as fair quality, and three were deemed poor quality across all domains. The main biases identified were insufficient sample size justification, lack of blinding of outcome assessors, and inadequate control for confounding variables. The detailed evaluations for each study can be seen in Supplementary Table S2.

Regarding publication bias and small-study effects, a funnel plot analysis was performed for each NPI domain in the unspecified VCI group since it was the only group with at least 10 observations. Significant asymmetry was only observed for elation/euphoria (bias estimate: -1.44, $p = 0.014$). For delusions (bias estimate: -1.28, $p = 0.062$), hallucinations (bias estimate: -1.06, $p = 0.124$), agitation/aggression (bias estimate: -0.17, $p = 0.828$), depression/dysphoria (bias estimate: -1.03, $p = 0.151$), anxiety (bias estimate: -0.36, $p = 0.565$), apathy/indifference (bias estimate: 1.60, $p = 0.077$), disinhibition (bias estimate: -0.87, $p = 0.237$), irritability/lability (bias estimate: -0.26, $p = 0.761$), aberrant motor behavior (bias estimate: -0.826, $p = 0.347$), sleep and nighttime behavior disorders (bias estimate: -1.60, $p = 0.073$), and appetite and eating disorders (bias estimate: -0.05, $p = 0.947$), no significant asymmetries were observed according to the Thompson-Sharp test. The funnel plots are shown in Supplementary Figure S1.

Sensitivity analysis

Sensitivity analysis by the leave-one-out method did not significantly modify the pooled prevalence of any BPSD independently of the group. To investigate the effect of heterogeneity on the results, we performed a second synthesis of the articles, this time omitting the study that most reduced the I^2 statistic in the sensitivity analysis for each BPSD. The results of each sensitivity analysis are presented in Supplementary Figure S2, and the second synthesis is compared with the first in Figure 2, with further details provided in Supplementary Table S3.

Meta-regression

A meta-regression analysis was performed for all NPI domains in the unspecified VCI group in search of significant associations between the logit-transformed prevalences and baseline characteristics of the sample, namely mean age, years of education, MMSE score, and CDR. Years of education correlated positively with the prevalence of agitation/aggression (R^2: 67.04%, slope: 0.088, $p < 0.001$) and disinhibition (R^2: 60.84%, slope: 0.137, $p = 0.010$). A significant association was also seen between the mean MMSE score and irritability/lability (R^2: 28.69%, slope: 0.115, $p = 0.007$). Although marginally non-significant, associations were also found between years of education and anxiety (R^2: 7.30%, slope: 0.090, $p = 0.060$) as well as elation/euphoria (R^2: 46.75%, slope: 0.087, $p = 0.069$). No other correlations were statistically significant (all $p > 0.05$). All meta-regression results can be found in Supplementary Figure S3.

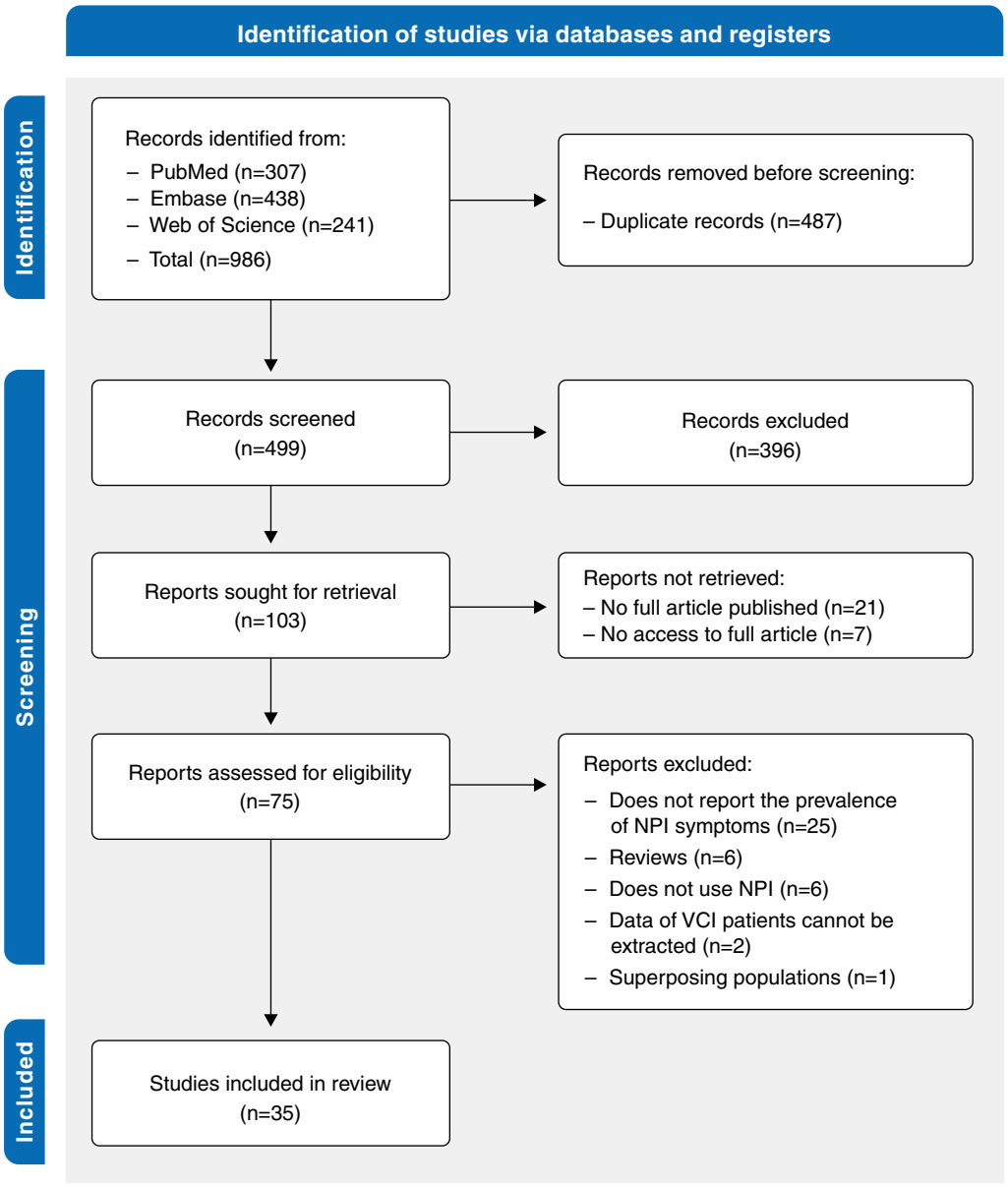


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram describing the process of screening and selection. NPI = Neuropsychiatric Inventory; VCI = vascular cognitive impairment.

Discussion

Our study is the first meta-analysis to compare different behavioral and psychological features across subtypes and stages of VCI. This research builds on a previous systematic review that examined BPSD across various VCI types.[7] However, we identified several studies published after that review that could expand the existing evidence base. Although numerous papers documented the presentation of these symptoms in cross-sectional studies, there was a gap in the literature of a convergent and extensive analysis of BPSD prevalence in VCI. As a result, the present work integrates multiple studies with a robust analytical approach and includes epidemiological aspects not covered in earlier studies. It makes a relevant contribution to the field by exploring the frequency of BPSD in 35 studies covering 5,805 individuals. Furthermore, we contrasted how the frequencies behaved among the different types of VCI (unspecified, subcortical, VCI-ND, and mixed pathologies), allowing us to discuss potential mechanisms to explain the heterogeneity of neuropsychiatric symptoms in VCI.

As a main result, our meta-analysis showed no significant differences in occurrence between BPSD within most groups of VCI. Noteworthy, VCI-ND prevalences differed from those of the unspecified VCI group for hallucinations and from those of all other groups regarding apathy/indifference, disinhibition, and agitation/aggression. Thus, it is reasonable to assume that these features do not indicate differential diagnosis among the

Table 1 Design and population characteristics of the included studies

Study	Design	Country	Type of VCI assessed	Patients (n)	Age (years)	Education (years)	MMSE	CDR	Quality
Akyol[29]	Cross-sectional	Turkey	Unspecified VaD	29	74.17±10.49	7.69±4.40	18.07±8.44	1.28±0.53	Fair
Alves[30]	Cross-sectional	Brazil	Subcortical VaD	20	75.35±7.31	7.40±4.84	21.00±5.70	NR	Fair
Amoo[31]	Cross-sectional	Nigeria	Unspecified VaD	18	64.50±8.70	NR	NR	NR	Fair
Amr[32]	Cross-sectional	Saudi Arabia	Unspecified VaD, mixed dementia	23	69.90±5.60	NR	16.70±5.50	1.91±0.79	Fair
Anor[33]	Cross-sectional	Canada	Unspecified VaD, mixed dementia	88	79.60±8.80	12.60±4.30	23.80±5.20	NR	Fair
Bandyopadhyay[34]	Cross-sectional	India	Unspecified VaD	50	59.58±6.56	12.06±2.53	15.48±2.47	1.89±0.65	Fair
Bhat[35]	Cross-sectional	India	Unspecified VaD	76	58.05±5.73	NR	NR	1.65±0.75	Fair
Caputo[4]	Cross-sectional	Italy	Unspecified VaD	131	77.90±6.90	5.60±4.20	15.00±6.20	1.98±0.63	Fair
Chiu[36]	Cross-sectional	Taiwan	Unspecified VaD, mixed dementia, VCI-ND	157	71.00±10.20	6.30±4.70	17.40±8.10	1.20±0.80	Poor
D'Onofrio[37]	Cross-sectional	Italy	Unspecified VaD	136	80.81±6.94	3.55±3.15	16.35±5.04	1.59±0.91	Fair
Fernández-Martínez[38]	Cross-sectional	Spain	Unspecified VaD	14	NR	NR	NR	NR	Fair
Fernández-Martínez[39]	Cross-sectional	Spain	Unspecified VaD, subcortical VaD	28	72.49±7.74	9.32±3.15	19.39±2.51	NR	Fair
Fonseca[40]	Cross-sectional	Brazil	Mixed dementia	14	75.10±7.60	NR	14.60±4.70	NR	Fair
Fuh[41]	Cross-sectional	Taiwan	Unspecified VaD, subcortical VaD	196	75.20±7.20	NR	14.90±7.10	NR	Fair
Gupta[42]	Cross-sectional	India	Unspecified VaD, VCI-ND	60	58.80±12.30	7.90±5.10	NR	NR	Fair
Hsieh[43]	Cross-sectional	Taiwan	Unspecified VaD	77	71.40±6.70	NR	16.20±5.10	1.36±0.49	Fair
Ikeda[44]	Cross-sectional	Japan	Unspecified VaD	28	81.00±5.90	NR	18.10±6.10	1.52±0.74	Fair
Johnson[3]	Cross-sectional	United States	Unspecified VaD, mixed dementia	177	74.40±8.30	12.80±3.80	NR	1.50±0.70	Fair
Jung[45]	Cross-sectional	South Korea	Subcortical VaD	48	71.80±7.20	8.50±4.80	21.60±4.40	0.85±0.74	Good
Kazui[46]	Cross-sectional	Japan	Unspecified VaD	191	75.90±10.0	10.80±2.70	19.60±5.00	1.22±0.72	Fair
Kim[47]	Cross-sectional	South Korea	Subcortical VaD, VCI-ND	127	73.80±6.90	8.90±5.30	23.30±4.83	NR	Good
Lyketsos[48]	Cross-sectional	United States	Unspecified VaD	62	NR	NR	NR	NR	Fair
Manso-Calderón[49]	Cross-sectional	Spain	Unspecified VaD, subcortical VaD	320	80.10±6.90	12.60±3.00	18.20±6.40	1.77±0.71	Fair
Mukherjee[50]	Cross-sectional	India	Unspecified VaD, mixed dementia	18	66.20±8.10	NR	NR	1.81±0.82	Fair
Perri[51]	Cross-sectional	Italy	Subcortical VaD	22	72.10±10.90	8.80±4.30	22.70±2.70	0.90±0.60	Fair
Porter[52]	Cross-sectional	United States	Unspecified VaD	43	75.10±9.80	12.80±4.20	19.50±6.90	NR	Poor
Ricci[53]	Cross-sectional	Italy	Unspecified VaD, mixed dementia	80	NR	NR	NR	NR	Fair
Santos[54]	Cross-sectional	Brazil	Unspecified VaD	53	76.70±9.40	NR	NR	1.87±0.67	Fair
Schwertner[55]	Cross-sectional	Sweden	Unspecified VaD	1,708	81.50±7.20	NR	20.10±4.90	NR	Fair
Sep[56]	Prospective cohort	Netherlands	Unspecified VaD	575	68.40±8.30	NR	25.80±2.80	0.68±0.37	Good
Siqueira-Neto[57]	Cross-sectional	Brazil	Unspecified VaD	234	67.77±10.35	2.84±2.96	13.22±7.00	NR	Fair
Srikanth[58]	Cross-sectional	India	Unspecified VaD	31	59.60±9.90	NR	17.60±4.70	1.70±0.50	Fair
Stakenborg[59]	Randomized controlled trial	Austria, Canada, France, Germany, Italy, Russia, Spain, Switzerland, United Kingdom, United States	Unspecified VaD	484	72.60±8.20	9.30±4.10	19.00±4.00	NR	Good
Xing[60]	Prospective cohort	China	Unspecified VaD	457	66.79±10.48	6.71±4.81	15.39±5.58	NR	Good
Yadav[61]	Cross-sectional	India	Unspecified VaD	30	75.50±6.70	NR	N.R	NR	Poor

CDR = Clinical Dementia Rating; MMSE = Mini Mental State Examination; NR = not reported; VaD = vascular dementia; VCI = vascular cognitive impairment; VCI-ND = vascular cognitive impairment-non-dementia.

Table 2 Pooled results for each NPI domain in each VCI group

VCI group/NPI domain	No. of patients	Frequency (per 100 observations)	95%CI	I^2	95%PI
General					
Delusions	4,527	19.31	15.26-24.12	90	5.80-48.18
Hallucinations	4,527	14.80	11.63-18.65	87	4.59-38.56
Agitation/aggression	4,937	37.61	32.08-43.48	92	15.00-67.31
Depression/dysphoria	4,858	43.48	38.41-48.68	89	21.59-68.24
Anxiety	4,900	33.85	29.51-38.48	86	16.24-57.45
Elation/euphoria	4,658	9.02	7.07-11.44	76	3.37-21.97
Apathy/indifference	4,994	54.29	47.22-61.19	94	20.75-84.35
Disinhibition	4,532	19.81	16.00-24.27	86	7.08-44.47
Irritability/lability	4,989	38.76	32.87-45.01	93	14.42-70.40
Aberrant motor behavior	4,851	21.42	16.43-27.43	94	4.99-58.61
Sleep and nighttime behavior disorders	4,350	38.43	31.55-45.80	94	12.93-72.40
Appetite and eating disorders	4,453	27.32	22.70-32.49	89	11.41-52.31
Subcortical					
Delusions	526	23.18	16.93-30.88	63	9.09-47.67
Hallucinations	526	15.48	9.64-23.92	70	3.75-46.28
Agitation/aggression	526	43.18	38.98-47.48	0	37.70-48.83
Depression/dysphoria	526	52.11	42.15-61.91	76	26.60-79.31
Anxiety	526	41.50	33.09-50.44	69	19.30-67.78
Elation/euphoria	506	8.72	5.25-14.14	51	2.21-28.78
Apathy/indifference	526	62.01	51.93-71.16	75	31.21-85.45
Disinhibition	526	25.91	22.34-29.83	0	21.30-31.12
Irritability/lability	526	44.73	35.11-54.6	76	18.59-74.14
Aberrant motor behavior	504	21.38	16.10-27.83	50	9.57-41.16
Sleep and nighttime behavior disorders	504	36.95	24.72-51.12	86	7.99-79.83
Appetite and eating disorders	504	34.16	28.37-40.46	39	20.87-50.50
Mixed					
Delusions	228	28.61	19.91-39.25	50	10.01-59.07
Hallucinations	228	26.64	15.50-41.81	72	4.13-75.38
Agitation/aggression	228	38.00	30.23-46.43	25	22.59-56.27
Depression/dysphoria	228	45.68	32.77-59.19	67	14.07-81.19
Anxiety	228	40.90	28.28-54.84	68	11.34-79.91
Elation/euphoria	186	8.49	5.17-13.63	0	2.81-22.95
Apathy/indifference	228	61.65	52.71-69.87	31	41.07-78.77
Disinhibition	193	22.44	15.34-31.60	29	8.12-48.65
Irritability/lability	228	40.44	32.44-48.98	26	24.29-58.97
Aberrant motor behavior	136	27.25	16.43-41.66	55	5.53-70.57
Sleep and nighttime behavior disorders	136	44.63	33.54-56.28	36	20.11-72.07
Appetite and eating disorders	136	25.82	19.00-34.07	0	16.60-37.85
VCI-ND					
Delusions	128	11.40	4.09-27.96	64	0.00-100.00
Hallucinations	69	2.95	0.74-11.04	0	-
Agitation/aggression	128	15.53	9.29-24.82	29	0.10-97.03
Depression/dysphoria	128	44.97	22.10-70.18	87	0.00-100.00
Anxiety	128	30.07	19.95-42.59	49	0.17-99.10
Elation/euphoria	69	4.96	1.60-14.34	0	-
Apathy/indifference	128	19.07	11.50-29.04	35	0.09-98.36
Disinhibition	128	7.20	3.79-13.28	0	0.10-86.36
Irritability/lability	128	32.75	23.85-43.09	27	1.03-95.80
Aberrant motor behavior	69	7.26	1.25-32.59	63	-
Sleep and nighttime behavior disorders	128	19.57	3.03-65.42	93	0.00-100.00
Appetite and eating disorders	128	25.14	12.31-44.55	76	0.00-99.99

95%PI = 95% prediction interval; NPI = Neuropsychiatric Inventory; VCI-ND = vascular cognitive impairment-non-dementia.

VCI types compared, especially within dementia groups. However, the isolated prevalence of each of these symptoms largely varied. That might indicate different underlying mechanisms for their development, and, in case of symptoms with high concurrent prevalences, such as apathy, depression, sleep disturbances, irritability, and agitation/aggression, superposing underlying mechanisms should be considered.

Agitation in AD has been theorized as a dysfunction associated with atrophy in the left insula and anterior cingulate cortex and overall neurodegeneration in the anterior salience network.[62,63] Meanwhile, resting-state functional magnetic resonance imaging (fMRI) analysis suggested agitation was linked to increased activity in the left superior cingulate and paracingulate gyri.[64] A previous cohort study correlated the impact of subcortical vascular insult on the occurrence of agitation, although the result was not statistically significant. Yet, the same study found an association between baseline temporal and frontal WMH and agitation severity score, indicating it

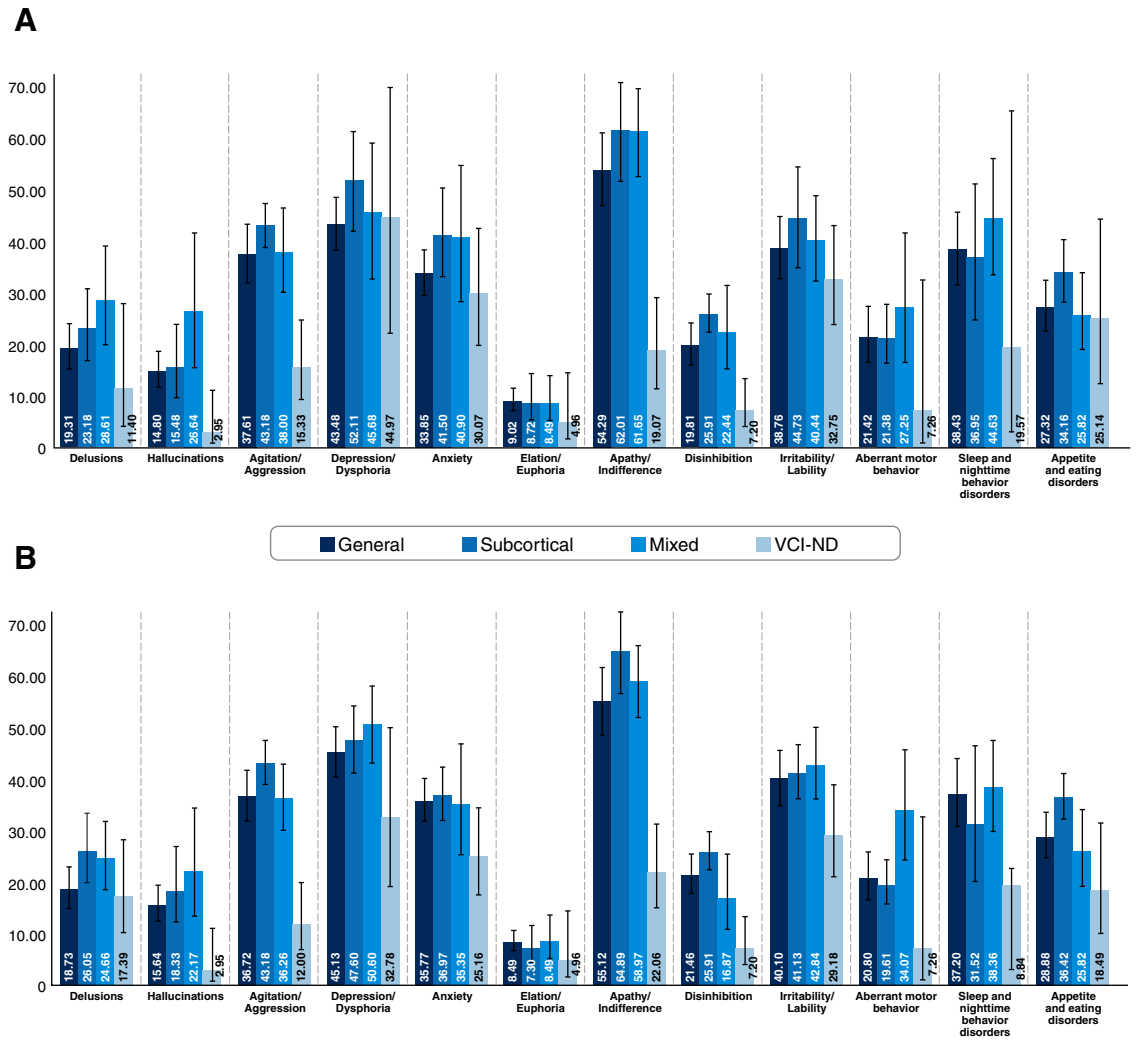


Figure 2 Bar plots with error bars comparing the frequencies and 95%CI of each NPI domain from the primary and secondary synthesis. A) Results from the primary synthesis. B) Results from the secondary synthesis. NPI = Neuropsychiatric Inventory; VCI-ND = vascular cognitive impairment-non-dementia.

can result from or increase with WM disruption.[33] Our results showed a high prevalence of agitation/aggression in subcortical VCI; therefore, further investigation into the role of subcortical circuits in agitation/aggression is necessary, with additional imaging research on specific WMH localization being crucial.

Our findings also support previous studies indicating that apathy can be due to subcortical disconnection related to vascular burden, as the prevalences of this symptom were high in the general VaD group and in the subcortical group, while being significantly lower for VCI-ND.[11-13] Since small-vessel disease (SVD) is the main contributor to VCI, the overall VCI prevalences are expected to reflect those of SVD.[65] The general VaD and subcortical groups' prevalences did not differ significantly from those of the mixed pathology group. This, and the significant prevalence of mixed pathology described in the literature, might corroborate the leading theories for the genesis of such diseases, such as "the two-hit hypothesis" proposed by Zlokovic in 2011, in which both AD and VCI might be connected disorders or have intricate pathophysiology. In this matter, our results support the idea that behavioral and psychological profiles cannot and should not be used to differentiate mixed dementias from pure VCI.[66,67]

Given that mixed pathology may not always be distinguished through clinical and radiological evaluation alone, we anticipate future research incorporating biomarkers indicative of degenerative processes – such as beta-amyloid and phosphorylated tau – will provide greater insight. This could facilitate accurate differentiation between patients with VaD and those with mixed dementia, thereby enhancing our understanding of the psychological and behavioral profiles associated with each condition.[68,69]

Regarding VCI, particularly SVD, disrupted functional connectivity (FC) in specific networks – the dorsal attention network (DAN), the default-mode network (DMN), and the frontoparietal control network (FPCN) – correlated with an increased degree of cognitive

impairment.[70] Neuroimaging studies specifically evaluating apathy in VCI have discussed whether it may occur as a syndrome apart from depression and cognitive decline, resulting from WM disconnection due to SVD.[71] A pathway analysis using diffusion tensor tractography showed that patients with apathy, but not depression, had reduced measures of network density and efficiency throughout the whole brain.[72] More recent research on comparative resting-state FC between SVD and AD patients further elaborates on this disconnection theory, showing distinct FC in the salience network in SVD. Specific regions, such as the middle frontal gyri and the anterior insula, were identified as central hubs for apathy genesis.[73]

Excluding outliers, which can skew the study results and increase heterogeneity, we found a noticeable prevalence of sleep and nighttime disorders across different stages of dementia. This is particularly evident in the VaD and mixed dementia groups, with a higher prevalence observed in those with mixed pathology. In this regard, prior research found that AD patients who experienced more sleep disturbances also had greater WMH.[15] This included a higher WMH load overall and specifically in the frontal and occipital regions. In parallel, a study examining WM in non-dementia patients with insomnia noted decreased integrity in the left thalamus and pars triangularis tracts.[74] Alterations in the ventrolateral preoptic area in the anterior hypothalamus and the suprachiasmatic nucleus have also been correlated with sleep changes in dementia.[75] These findings suggest that sleep disturbances could be associated with vascular burden and WM disconnection. However, other environmental and psychological aspects might also predispose to sleep alterations independent of structural changes.[76]

The relatively low frequency of hallucinations in both general VaD and VCI-ND can be attributed to the selective nature of the vascular pathology. Psychotic symptoms are more common in diseases such as LBD and Parkinson's disease dementia, with a complex neurobiology that involves dysfunction in the dopaminergic and cholinergic systems and deafferentation of posterior cortical areas linked to perceptual processing.[77] That contrasts with the mixed-dementia group, where hallucinations were more prevalent in absolute terms. The co-occurrence of AD, which often affects perceptual regions like the temporoparietal cortex and visual association areas, might exacerbate perceptual symptoms. In the subcortical group, hallucinations could be linked to the selective involvement of subcortical structures, such as the thalamus and basal ganglia, and even the connections between posterior associative areas that contribute to sensory integration and cognitive processing.[77] Disruption of these circuits could result in perceptual disturbances less frequently than in dementias with primarily dopaminergic involvement.[78] As previously described, vascular lesions to the cortex and disruption of subcortical networks, leading to remote alterations such as a reduction in grey-matter volume and subsequent disruption of the functional interconnectivity of the thalamus, limbic, paralimbic, and other subcortical structures, might account for such perceptual disturbances and generate psychotic symptoms.[70,79,80] In general, although previous studies reported an association of cerebral amyloid angiopathy (CAA) and SVD with psychotic symptoms in AD, the contribution of vascular pathology to this phenomenon in dementia requires further investigation.[79]

In VCI-ND, apathy, disinhibition, hallucinations, and agitation/aggression rates were significantly lower than in other groups, which suggests an association of these symptoms with dementia progression and increased vascular burden. However, we must stress that the small number of studies addressing VCI-ND and their relatively small sample sizes might constitute a limitation. Beyond that, this observation could be further elucidated by comparing groups with varying levels of vascular load and cognitive impairment, as measured by the Fazekas scale.[81] Depression was a widespread symptom across every group. Fang et al.[82] found that SVD features might increase the risk for incident depression. Moreover, alongside molecular, inflammatory, and endothelial-dysfunction mechanisms, some studies support depression as a result of damage to frontal-subcortical circuits.[83-85] An fMRI study with depressed SVD patients revealed that these individuals' brains have unstable dynamic FC states, alongside hyperconnectivity in the lateral visual network and reduced connectivity between the ventral attention network and the sensorimotor network. The high prevalence of depression in VCI-ND might reflect an early dysfunction of these networks and circuits.[86] In this context, we believe that vascular risk factors and cerebrovascular disease could precipitate the development of depression, as predicted in the vascular depression hypothesis.[11] The persistence of this symptom across dementia stages also corroborates studies indicating that greater WMH is associated with worsening depressive states and poorer response to antidepressants.[87-90]

Regarding the correlation with cognitive decline, our meta-regression revealed that lower MMSE scores are not associated with a higher prevalence of BPSD other than irritability/lability. In that respect, a cross-sectional study of cognitively unimpaired older adults with severe WMH found that the odds of having elation, disinhibition, agitation, and anxiety were higher compared to groups with less WMH.[91] Interestingly, in our study, years of education correlated positively with the prevalence of agitation/aggression, anxiety, euphoria, and disinhibition. Few studies have investigated the relationship between education and the severity of neuropsychiatric symptoms in dementia.[92-94] Although cognitive reserve has been associated with less deleterious effects of neurodegenerative pathology in cognition, the same could not be said for BPSD.[95] In contrast to our results, a multivariate analysis found years of education (as a proxy of cognitive reserve) may attenuate the severity of affective and behavioral symptoms in dementia.[92]

Our study has limitations that must be taken into account. The absence of a control group is a notable shortcoming, especially considering the high prevalence of mood disorders among older adults, regardless of cognitive status.[96] Furthermore, the limited number of longitudinal studies hindered our ability to accurately

capture the timing of symptom onset during disease progression. Also, the sample size of patients with VCI-ND was relatively small. Additionally, the reviewers did not search grey literature, which may have led to the omission of relevant unpublished or non-indexed studies. Given that cerebrovascular disease represents a continuum that may affect patients over many decades, it is crucial that studies longitudinally approach BPSD that may arise in this continuum, including before the onset of cognitive symptoms. It is noteworthy that the NPI is a subjective questionnaire; therefore, it is subject to information bias. Since it was developed to assess dementia patients, it may not be the most accurate tool for those with VCI-ND.

To address the trajectory of BPSD across the spectrum of VCI, especially within VCI-ND, we recommend that future studies prioritize longitudinal designs. Accurate differentiation between VCI subtypes and mixed pathology might require integrating neuroimaging with biomarkers indicative of neurodegenerative processes, complemented by thorough, detailed cognitive assessments. Additionally, exploration of the mechanisms underlying specific BPSD through functional neuroimaging is crucial for elucidating the basis for these symptoms' heterogeneity and for developing targeted therapeutic strategies.

To date, studies have most consistently utilized the NPI to assess the presence of neuropsychiatric symptoms. Scales evaluating the presence of BPSD more comprehensively, such as the Cohen-Mansfield Agitation Inventory (CMAI), which assesses 29 behavioral changes commonly observed in dementias, may provide more detailed information regarding the neuropsychiatric profile of patients across different forms of VCI.[97] This tool was not consistently explored in the studies included in our review, so validating this inventory in populations with VCI may support its inclusion in future research. Finally, the impact of vascular risk factors, extent of cerebrovascular disease (as quantified by objective measures), and individual characteristics (including educational attainment) on the occurrence and severity of BPSD requires further investigation, possibly including control groups of cognitively unimpaired older adults.

In this systematic review and meta-analysis, we elucidated the prevalence of BPSD across different types of VCI. There were no significant differences in occurrence between BPSD within most groups of VCI. Notably, the prevalences seen in the VCI-ND group differed from those of the unspecified VCI group for hallucinations and from those seen in all other groups for apathy/indifference, disinhibition, and agitation/aggression. In mixed dementia, hallucinations (26.64%) and sleep and nighttime disorders (44.63%) were more prevalent than in other VCI types.

Longitudinal follow-up of patients from the earliest stages of VCI, along with comparisons between individuals at different stages of cerebrovascular disease, will deepen our understanding of how these symptoms develop throughout the continuum of cerebrovascular disease.

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Data availability

All data are available within the manuscript and its supplementary files.

Disclosure

The authors report no conflicts of interest.

Author contributions

APS: Data curation; Writing – original draft
AOML: Data curation; Writing – original draft
CBALS: Data curation; Writing – original draft
MGNCC: Data curation; Writing – original draft
MMCR: Data curation; Writing – original draft
AEOR: Data curation; Writing – original draft
SMS: Data curation; Writing – original draft
BHCCF: Data curation; Writing – review & editing
SWJ: Data curation; Writing – review & editing
ESM: Writing – review & editing
BJAPB: Supervision; Conceptualization; Project administration; Writing – review & editing
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References

1 Reuben DB, Kremen S, Maust DT. Dementia prevention and treatment: a narrative review. JAMA Intern Med. 2024;184:563-72.
2 Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. Behavioral and psychological symptoms of dementia. Front Neurol. 2012;3:73.
3 Johnson DK, Watts AS, Chapin BA, Anderson R, Burns JM. Neuropsychiatric profiles in dementia. Alzheimer Dis Assoc Disord. 2011; 25:326-32.
4 Caputo M, Monastero R, Mariani E, Santucci A, Mangialasche F, Camarda R, et al. Neuropsychiatric symptoms in 921 elderly subjects with dementia: a comparison between vascular and neurodegenerative types. Acta Psychiatr Scand. 2008;117:455-64.
5 Skrobot OA, O'Brien J, Black S, Chen C, DeCarli C, Erkinjuntti T, et al. The Vascular Impairment of Cognition Classification Consensus Study. Alzheimers Dement J Alzheimers Assoc. 2017;13:624-33.
6 Barbosa BJAP, Siqueira JI, Alves GS, Sudo FK, Suemoto CK, Tovar-Moll F, et al. Diagnosis of vascular cognitive impairment: recommendations of the scientific department of cognitive neurology and aging of the Brazilian Academy of Neurology. Dement Neuropsychol. 2022;16:53-72.
7 Tiel C, Sudo FK, Alves GS, Ericeira-Valente L, Moreira DM, Laks J, et al. Neuropsychiatric symptoms in vascular cognitive impairment: a systematic review. Dement Neuropsychol. 2015;9:230-6.
8 Aizenstein HJ, Andreescu C, Edelman KL, Cochran JL, Price J, Butters MA, et al. fMRI correlates of white matter hyperintensities in late-life depression. Am J Psychiatry. 2011;168:1075-82.
9 Clancy U, Gilmartin D, Jochems ACC, Knox L, Doubal FN, Wardlaw JM. Neuropsychiatric symptoms associated with cerebral small

vessel disease: a systematic review and meta-analysis. Lancet Psychiatry. 2021;8:225-36.
10 Brookes RL, Herbert V, Lawrence AJ, Morris RG, Markus HS. Depression in small-vessel disease relates to white matter ultrastructural damage, not disability. Neurology. 2014;83:1417-23.
11 Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. Mol Psychiatry. 2013;18:963-74.
12 Ozzoude M, Varriano B, Beaton D, Ramirez J, Adamo S, Holmes MF, et al. White matter hyperintensities and smaller cortical thickness are associated with neuropsychiatric symptoms in neurodegenerative and cerebrovascular diseases. Alzheimers Res Ther. 2023;15:114.
13 Lisiecka-Ford DM, Tozer DJ, Morris RG, Lawrence AJ, Barrick TR, Markus HS. Involvement of the reward network is associated with apathy in cerebral small vessel disease. J Affect Disord. 2018; 232:116-21.
14 Khalaf A, Edelman K, Tudorascu D, Andreescu C, Reynolds CF, Aizenstein H. White matter hyperintensity accumulation during treatment of late-life depression. Neuropsychopharmacology. 2015; 40:3027-35.
15 Kamal F, Morrison C, Dadar M. Investigating the relationship between sleep disturbances and white matter hyperintensities in older adults on the Alzheimer's disease spectrum. Alzheimers Dement Amst Neth. 2024;16:e12553.
16 Clancy U, Ramirez J, Chappell FM, Doubal FN, Wardlaw JM, Black SE. Neuropsychiatric symptoms as a sign of small vessel disease progression in cognitive impairment. Cereb Circ Cogn Behav. 2022; 3:100041.
17 Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
18 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Revised Edition (DSM-III-R). Washington: American Psychiatric Association; 1987.
19 Pull CB. [DSM-IV]. Encephale. 1995;21 Spec No 5:15-20.
20 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington: American Psychiatric Publishing; 2013.
21 Erkinjuntti T. Clinical criteria for vascular dementia: the NINDS-AIREN criteria. Dement Basel Switz. 1994;5:189-92.
22 Cummings J. The Neuropsychiatric Inventory: development and applications. J Geriatr Psychiatry Neurol. 2020;33:73-84.
23 Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5:210.
24 Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
25 National Heart, Lung, and Blood Institute. Assessing cardiovascular risk: systematic evidence review from the Risk Assessment Work Group. 2023 Nov [cited 2025 Apr 20]. https://www.nhlbi.nih.gov/health-topics/assessing-cardiovascular-risk
26 Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. Stat Med. 1999;18:2693-708.
27 Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health. 2019;22:153-60.
28 Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60.
29 Akyol MA, Küçükgüçlü Ö, Yener G. Investigation of factors affecting apathy in three major types of dementia. Noro Psikiyatri Arsivi. 2020; 57:120-5.
30 Alves GS, Alves CEO, Lanna MEO, Ericeira-Valente L, Sudo FK, Moreira D, et al. Clinical characteristics in subcortical ischemic white matter disease. Arq Neuropsiquiatr. 2009;67:173-8.
31 Amoo G, Akinyemi RO, Onofa LU, Akinyemi JO, Baiyewu O, Ogunlesi AO, et al. Profile of clinically-diagnosed dementias in a neuropsychiatric practice in Abeokuta, south-western Nigeria. Afr J Psychiatry. 2011;14:377-82.
32 Amr M, El-Gilany A-H, Sallam K, Shams T. Characteristics of patients with dementia attended in a tertiary outpatient clinic in Eastern Region, Saudi Arabia. J Psychiatry. 2014;17.
33 Anor CJ, Dadar M, Collins DL, Tartaglia MC. The longitudinal assessment of neuropsychiatric symptoms in mild cognitive impairment and Alzheimer's disease and their association with white matter hyperintensities in the National Alzheimer's Coordinating Center's uniform data set. Biol Psychiatry Cogn Neurosci Neuroimaging. 2021;6:70-8.
34 Bandyopadhyay TK, Biswas A, Roy A, Guin DS, Gangopadhyay G, Sarkhel S, et al. Neuropsychiatric profiles in patients with Alzheimer's disease and vascular dementia. Ann Indian Acad Neurol. 2014; 17:325-30.
35 Bhat A, Biswas A, Das G, Lahiri D, Dubey S, Mukherjee A. Behavioral variations among vascular cognitive impairment subtypes – A comparative study. Appl Neuropsychol Adult. 2023;30:439-46.
36 Chiu P-Y, Liu C-H, Tsai C-H. Neuropsychiatric manifestations in vascular cognitive impairment patients with and without dementia. Acta Neurol Taiwanica. 2007;16:86-91.
37 D'Onofrio G, Sancarlo D, Panza F, Copetti M, Cascavilla L, Paris F, et al. Neuropsychiatric symptoms and functional status in Alzheimer's disease and vascular dementia patients. Curr Alzheimer Res. 2012;-9:759-71.
38 Martínez MF, Flores JC, Pérez de las Heras S, Lekumberri AM, Menocal MG, Imirizaldu JJZ. Prevalence of neuropsychiatric symptoms in elderly patients with dementia in Mungialde County (Basque Country, Spain). Dement Geriatr Cogn Disord. 2008;25: 103-8.
39 Fernández-Martínez M, Castro J, Molano A, Zarranz JJ, Rodrigo RM, Ortega R. Prevalence of neuropsychiatric symptoms in Alzheimer's disease and vascular dementia. Curr Alzheimer Res. 2008;5:61-9.
40 Fonseca SR, Santos APB, Almeida MA, Guimarães HC, Corrêa TAF, Beato RG, et al. Perfil neuropsiquiátrico na doença de Alzheimer e na demência mista. J Bras Psiquiatr. 2008;57:117-21.
41 Fuh J-L, Wang S-J, Cummings JL. Neuropsychiatric profiles in patients with Alzheimer's disease and vascular dementia. J Neurol Neurosurg Psychiatry. 2005;76:1337-41.
42 Gupta M, Dasgupta A, Khwaja GA, Chowdhury D, Patidar Y, Batra A. The profile of behavioral and psychological symptoms in vascular cognitive impairment with and without dementia. Ann Indian Acad Neurol. 2013;16:599-602.
43 Hsieh C-J, Chang C-C, Lin C-C. Neuropsychiatric profiles of patients with Alzheimer's disease and vascular dementia in Taiwan. Int J Geriatr Psychiatry. 2009;24:570-7.
44 Ikeda M, Fukuhara R, Shigenobu K, Hokoishi K, Maki N, Nebu A, et al. Dementia associated mental and behavioural disturbances in elderly people in the community: findings from the first Nakayama study. J Neurol Neurosurg Psychiatry. 2004;75:146-8.
45 Jung N-Y, Kim HJ, Kim YJ, Kim S, Seo SW, Kim E-J, et al. Neuropsychiatric characteristics of PiB-negative subcortical vascular dementia versus behavioral variant frontotemporal dementia. Arch Gerontol Geriatr. 2016;67:86-91.
46 Kazui H, Yoshiyama K, Kanemoto H, Suzuki Y, Sato S, Hashimoto M, et al. Differences of behavioral and psychological symptoms of dementia in disease severity in four major dementias. PloS One. 2016;11:e0161092.
47 Kim HJ, Kang SJ, Kim C, Kim GH, Jeon S, Lee JM, et al. The effects of small vessel disease and amyloid burden on neuropsychiatric symptoms: a study among patients with subcortical vascular cognitive impairments. Neurobiol Aging. 2013;34:1913-20.
48 Lyketsos CG, Steinberg M, Tschanz JT, Norton MC, Steffens DC, Breitner JC. Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. Am J Psychiatry. 2000;157:708-14.
49 Manso-Calderón R, Cacabelos-Pérez P, Sevillano-García MD, Herrero-Prieto ME, González-Sarmiento R. The impact of vascular burden on behavioural and psychological symptoms in older adults with dementia: the BEVASDE study. Neurol Sci. 2020;41:165-74.
50 Mukherjee A, Biswas A, Roy A, Biswas S, Gangopadhyay G, Das SK. Behavioural and psychological symptoms of dementia: correlates and impact on caregiver distress. Dement Geriatr Cogn Disord Extra. 2017;7:354-65.
51 Perri R, Monaco M, Fadda L, Caltagirone C, Carlesimo GA. Neuropsychological correlates of behavioral symptoms in Alzheimer's disease, frontal variant of frontotemporal, subcortical vascular, and lewy body dementias: a comparative study. J Alzheimers Dis. 2014; 39:669-77.
52 Porter VR, Buxton WG, Fairbanks LA, Strickland T, O'Connor SM, Rosenberg-Thompson S, et al. Frequency and characteristics of

anxiety among patients with Alzheimer's disease and related dementias. J Neuropsychiatry Clin Neurosci. 2003;15:180-6.
53 Ricci G, Cosso P, Leonetti A, Pagliari P, Ianes A. Behavioural and psychological symptoms of dementia: Study of a sample of elderly living in a nursing home. G Gerontol. 2009;57:70-7.
54 Santos MAO, Bezerra LS, Correia CC, Bruscky IS. Neuropsychiatric symptoms in vascular dementia: Epidemiologic and clinical aspects. Dement Neuropsychol. 2018;12:40-4.
55 Schwertner E, Pereira JB, Xu H, Secnik J, Winblad B, Eriksdotter M, et al. Behavioral and psychological symptoms of dementia in different dementia disorders: a large-scale study of 10,000 individuals. J Alzheimers Dis. 2022;87:1307-18.
56 Sep YCP, Leeuwis AE, Exalto LG, Boomsma JM, Prins ND, Verwer JH, et al. Neuropsychiatric symptoms as predictor of poor clinical outcome in patients with vascular cognitive impairment. Am J Geriatr Psychiatry. 2022;30:813-24.
57 Siqueira-Neto JI, Pontes-Neto OM, Vale FAC, Santos JV, Sales PMG, Santos JV, et al. Neuropsychiatric symptoms (NPS) in patients with pure vascular dementia (VaD) and mixed dementia (MD) from a memory outpatient clinic in Southeast Brazil. Dement Neuropsychol. 2013;7:263-8.
58 Srikanth S, Nagaraja AV, Ratnavalli E. Neuropsychiatric symptoms in dementia-frequency, relationship to dementia severity and comparison in Alzheimer's disease, vascular dementia and frontotemporal dementia. J Neurol Sci. 2005;236:43-8.
59 Staekenborg SS, Su T, van Straaten ECW, Lane R, Scheltens P, Barkhof F, et al. Behavioural and psychological symptoms in vascular dementia; differences between small- and large-vessel disease J Neurol Neurosurg Psychiatry. 2010;81:547-51.
60 Xing Y, Wei C, Chu C, Zhou A, Li F, Wu L, et al. Stage-specific gender differences in cognitive and neuropsychiatric manifestations of vascular dementia. Am J Alzheimers Dis Other Demen. 2012;27: 433-8.
61 Yadav N, Suthar S, Jain S. Clinical aspects of behavioural and psychological symptoms in vascular dementia. Arch Psychiatry Res. 2023;59:179-84.
62 Bruen PD, McGeown WJ, Shanks MF, Venneri A. Neuroanatomical correlates of neuropsychiatric symptoms in Alzheimer's disease. Brain J Neurol. 2008;131:2455-63.
63 Trzepacz PT, Yu P, Bhamidipati PK, Willis B, Forrester T, Tabas L, et al. Frontolimbic atrophy is associated with agitation and aggression in mild cognitive impairment and Alzheimer's disease. Alzheimers Dement J Alzheimers Assoc. 2013;9:S95-S104.e1.
64 Raczek M, Cercignani M, Banerjee S. Voxel-based morphometry and resting state fMRI as predictors of neuropsychiatric symptoms in Alzheimer's disease: neuropsychiatry and behavioral neurology/ neuropsychiatry. Alzheimers Dement. 2020;16.
65 Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. Lancet Neurol. 2019;18:684-96.
66 Sweeney MD, Sagare AP, Zlokovic BV. Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat Rev Neurol. 2018;14:133-50.
67 Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci. 2011;12: 723-38.
68 Ma W, Zhang J, Xu J, Feng D, Wang X, Zhang F. Elevated levels of serum neurofilament light chain associated with cognitive impairment in vascular dementia. Dis Markers. 2020;2020:6612871.
69 Peters N. Neurofilament light chain as a biomarker in cerebral small-vessel disease. Mol Diagn Ther. 2022;26:1-6.
70 Telgte AT, van Leijsen EMC, Wiegertjes K, Klijn CJM, Tuladhar AM, Leeuw F-E. Cerebral small vessel disease: from a focal to a global perspective. Nat Rev Neurol. 2018;14:387-98.
71 Wouts L, Marijnissen RM, Voshaar RCO, Beekman ATF. Strengths and weaknesses of the vascular apathy hypothesis: a narrative review. Am J Geriatr Psychiatry. 2023;31:183-94.
72 Tay J, Tuladhar AM, Hollocks MJ, Brookes RL, Tozer DJ, Barrick TR, et al. Apathy is associated with large-scale white matter network disruption in small vessel disease. Neurology. 2019;92:e1157-67.
73 Altunkaya S, Huang S-M, Hsu Y-H, Yang J-J, Lin C-Y, Kuo L-W, et al. Dissociable functional brain networks associated with apathy in subcortical ischemic vascular disease and Alzheimer's disease. Front Aging Neurosci. 2021;13:717037.
74 Kang JM, Joo SW, Son Y-D, Kim H, Ko K-P, Lee JS, et al. Low white-matter integrity between the left thalamus and inferior frontal gyrus in patients with insomnia disorder. J Psychiatry Neurosci JPN. 2018; 43:366-74.
75 Wennberg AMV, Wu MN, Rosenberg PB, Spira AP. Sleep disturbance, cognitive decline, and dementia: a review. Semin Neurol. 2017;37:395-406.
76 Molano J, Vaughn BV. Approach to insomnia in patients with dementia. Neurol Clin Pract. 2014;4:7-15.
77 O'Brien J, Taylor JP, Ballard C, Barker RA, Bradley C, Burns A, et al. Visual hallucinations in neurological and ophthalmological disease: pathophysiology and management. J Neurol Neurosurg Psychiatry. 2020;91:512-9.
78 El Haj M, Roche J, Jardri R, Kapogiannis D, Gallouj K, Antoine P. Clinical and neurocognitive aspects of hallucinations in Alzheimer's disease. Neurosci Biobehav Rev. 2017;83:713-20.
79 Ting SKS, Hao Y, Chia PS, Tan E-K, Hameed S. Clinicopathological correlation of psychosis and brain vascular changes in Alzheimer's disease. Sci Rep. 2016;6:20858.
80 Ogawa Y, Hashimoto M, Yatabe Y, Kaneda K, Honda K, Yuuki S, et al. Association of cerebral small vessel disease with delusions in patients with Alzheimer's disease. Int J Geriatr Psychiatry. 2013; 28:18-25.
81 Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol. 1987;149:351-6.
82 Fang Y, Qin T, Liu W, Ran L, Yang Y, Huang H, et al. Cerebral small-vessel disease and risk of incidence of depression: a meta-analysis of longitudinal cohort studies. J Am Heart Assoc. 2020;9:e016512.
83 Santos M, Xekardaki A, Kövari E, Gold G, Bouras C, Giannakopoulos P. Microvascular pathology in late-life depression. J Neurol Sci. 2012;322:46-9.
84 Yang S, Hua P, Shang X, Cui Z, Zhong S, Gong G, et al. A significant risk factor for poststroke depression: the depression-related subnetwork. J Psychiatry Neurosci JPN. 2015;40:259-68.
85 van Velzen LS, Kelly S, Isaev D, Aleman A, Aftanas LI, Bauer J, et al. White matter disturbances in major depressive disorder: a coordinated analysis across 20 international cohorts in the ENIGMA MDD working group. Mol Psychiatry. 2020;25:1511-25.
86 Xu J, Chen H, Hu Z, Ke Z, Qin R, Chen Y, et al. Characteristic patterns of functional connectivity-mediated cerebral small vessel disease-related cognitive impairment and depression. Cereb Cortex N Y N 1991. 2024;34:bhad468.
87 Alexopoulos GS, Bruce ML, Silbersweig D, Kalayam B, Stern E. Vascular depression: a new view of late-onset depression. Dialogues Clin Neurosci. 1999;1:68-80.
88 Salo KI, Scharfen J, Wilden ID, Schubotz RI, Holling H. Confining the concept of vascular depression to late-onset depression: a meta-analysis of MRI-defined hyperintensity burden in major depressive disorder and bipolar disorder. Front Psychol. 2019;10:1241.
89 Gerlach AR, Karim HT, Peciña M, Ajilore O, Taylor WD, Butters MA, et al. MRI predictors of pharmacotherapy response in major depressive disorder. Neuroimage Clin. 2022;36:103157.
90 Steffens DC, Krishnan KRR, Crump C, Burke GL. Cerebrovascular disease and evolution of depressive symptoms in the cardiovascular health study. Stroke. 2002;33:1636-44.
91 Liampas I, Siokas V, Zoupa E, Kyriakoulopoulou P, Stamati P, Provatas A, et al. Neuropsychiatric symptoms and white matter hyperintensities in older adults without dementia. Int Psychogeriatr. 2024;36:1051-63.
92 Kwak S, Park S, Kim J, Park S, Lee J-Y. Multivariate neuroanatomical correlates of behavioral and psychological symptoms in dementia and the moderating role of education. NeuroImage Clin. 2020;28:102452.
93 Lin C, Huang C-M, Fan Y-T, Liu H-L, Chen Y-L, Aizenstein HJ, et al. Cognitive reserve moderates effects of white matter hyperintensity on depressive symptoms and cognitive function in late-life depression. Front Psychiatry. 2020;11:249.
94 Chang-Quan H, Zheng-Rong W, Yong-Hong L, Yi-Zhou X, Qing-Xiu L. Education and risk for late life depression: a meta-analysis of published literature. Int J Psychiatry Med. 2010;40:109-24.
95 Stern Y, Arenaza-Urquijo EM, Bartrés-Faz D, Belleville S, Cantilon M, Chetelat G, et al. Whitepaper: defining and investigating cognitive

reserve, brain reserve, and brain maintenance. Alzheimers Dement J Alzheimers Assoc. 2020;16:1305-11.

96 Sjöberg L, Karlsson B, Atti A-R, Skoog I, Fratiglioni L, Wang H-X. Prevalence of depression: comparisons of different depression definitions in population-based samples of older adults. J Affect Disord. 2017;221:123-31.

97 Cohen-Mansfield J. Instruction manual for the Cohen-Mansfield Agitation Inventory (CMAI). Maryland: Research Institute of the Hebrew Home of Greater Washington; 1991 [cited 2025 Jul 1]. https://www.dementiaresearch.org.au/wp-content/uploads/2016/06/CMAI_Manual.pdf